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Please cite this article as https://doi.org/10.4097/kja.20509
Title Page

① Title:
Effect of etomidate use on ICU patients with ventilator therapy: A study of 12,526 patients in an open database from a single-center.

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③ Running title:
Etomidate in ICU patients

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⑤ Previous presentation in conferences:
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⑥ Funding and Conflict of interest
Author Younsuk Lee and Chi-Yeon Lim has been receiving 2018–2020 R&D Fund from the Korean Government (Ministry of Trade, Industry, and Energy). The remaining authors have disclosed that they have no conflicts of interests

⑦ Acknowledgments: Not applicable

⑧ IRB number: Not applicable

⑨ Clinical trial registration number: Not applicable
Effect of etomidate use on ICU patients with ventilator therapy: a study of 12,526 patients in an open database from a single-center

Running title: Effect of etomidate use on ICU patients
Abstract

Background: The safety issue regarding the use of etomidate is still a matter of dispute. We evaluated the effect of etomidate on mortality using a large cohort of critical care patients.

Methods: It was a retrospective matched cohort study at the Medical Information Mart for Intensive Care version 3 (MIMIC-III) database. Among 12,526 adult patients who were prescribed with etomidate or propofol on the start day of mechanical ventilation, 625 patients given etomidate were statistically matched with 6,250 patients given propofol. The primary outcome measures were the all-cause in-hospital mortality, along with 3 measures including 48-hour survival, cardiovascular morbidity, and infectious morbidity. An analysis to find out dose-mortality relationship of the etomidate was done using logistic regression with stepwise-selection of variables.

Results: All-cause in-hospital mortality was 1.84 times higher in the etomidate cohort (odds ratio, 1.84 [98.75% CI; 1.42, 2.37]). The odds for the first 48-hour survival was 57% lower in the etomidate cohort (0.43 [0.27, 0.73]). Odds for cardiovascular morbidity was not significantly lower in the etomidate cohort (0.86 [0.66, 1.12]) than the propofol cohort. Infectious morbidity was 1.77 times higher in the etomidate cohort (1.77 [1.35, 2.31]). The odds for death per 0.1 mg/kg of etomidate was estimated as 1.36 times higher (1.36 [95% CI 1.23, 1.49]).

Conclusions: Etomidate is not a wise choice as the hypnotic drug on the day of starting mechanical ventilation, as it is associated with the increased all-cause mortality in a dose-dependent manner, while not improving the first 48-hr survival.

Keywords: Dose-response relationship; Etomidate; Intensive care unit; Mortality; Propofol; Ventilator.
Introduction

Etomidate used for tracheal intubation in septic patients is known to be not associated with higher mortality [1]. However, some meta-analysis summarized the high association between mortality and the use of etomidate for tracheal intubation in patients with sepsis [2], and higher mortality rate is shown in critically ill patients with etomidate than comparator anesthetic induction agents [3]. The etomidate has also been reported to be associated with increased 30-day mortality when administered during anesthesia for patients who underwent non-cardiac surgery [4]. Conversely, Wagner et al. [5] showed no association between etomidate exposure and fewer poor outcomes including mortality in patients who underwent cardiac surgery. Much of disparate answers to this same question has seemed by no means to shrink until now.

Rather than making an uneasy blend of such disputes or adding a piece of not-so-new evidence onto the knowledge already piled up, we tried to meet answers to the most pressing problems facing our conflicts by discovering the dose-response relationship between etomidate exposure and mortality. Medical Information Mart for Intensive Care version 3 (MIMIC-III) is the database of combined real-world health records for medical records, prescriptions, dictionaries, diagnostic information including the disease-related groups, and the complete survival and death information of patients admitted to intensive care units in a hospital located in Boston, Massachusetts. Through accessing to data, we could design the retrospective study. Our interest has been focused on finding evidence of a biological gradient that existed between the dose of etomidate and death. We designed this study in a hope that a qualified vast amount of data in the MIMIC-III dataset could help us finding the dose-response relationship.
Materials and Methods

Construction of Cohorts

The MIMIC-III is an open database of electronic health records of critical care admissions to a tertiary care hospital in Boston, Massachusetts, the Beth Israel Deaconess Medical Center [6]. It comprises 38,597 adult patients (> 16-years) from 2001 to 2012. The use of deidentified MIMIC-III data for the current study has been deemed as not-human subject research by the institutional review boards at both University of Massachusetts Medical School, which is autonomically waived in the local ethics committee. Therefore, completing the required training course, all of our co-authors had grant to access to the MIMIC-III and use freely without an additional IRB approval. The selection of patients in the etomidate cohort and the propofol cohort was based on the following conditions.

- Common inclusion criteria: adult patients treated with a mechanical ventilator at least for 1 hour.
- Etomidate cohort: patients having a prescription of etomidate (20 mg or less) at the initial day of mechanical ventilation (referred to the “cohort start-date”).
- Propofol cohort: patients having a prescription of propofol instead of etomidate at the initial day of mechanical ventilation. The patients never had prescriptions of etomidate during the admission.

General exclusion criteria included patients having a history of the previous hospitalization within 7 days prior and having body weight or height beyond lower or upper 0.1 percentiles. A total of 12,526 patients were enrolled in the “before-matching cohorts” (Etomidate n = 625 vs. Propofol n = 11,901).

Matching
The before-matching patients were matched with the propensity to incline to the use of etomidate. We could minimize the heterogeneity of the patients obtained from the retrospective design of the study by mobilizing the matched cohorts. Matching procedure used the total of 43 variables including 9 physical characteristics, 4 clinical features, and 30 disease components of Elixhauser comorbidity [7, 8] as covariates for calculating the propensity scores. The nine physical characteristics were gender, 3 age-groups, 4 BMI-groups, and ethnicity. The four clinical features were hypothalamic adrenal insufficiency as a primary diagnosis, previous history of any of the adrenal suppressants (ketoconazole, metyrapone, suramin, aminoglutethimide, carbamazepine, phenobarbital, phenytoin, rifampin, and mitotane), admissions before mid-2008, and high SOFA score (> 5.0). Adopting the “nearest neighbor matching” method, 1:10 matching ratio, and targeting the absolute values of standardized differences being suppressed below 0.1, a total of 6,875 patients were assigned to one of the after-matching etomidate cohorts (n = 625) or the propofol cohort (n = 6,250) (Supplemental Digital Content 1).

**Primary Outcome Measures**

All-cause in-hospital mortality, incidence of the first 48-hour survival, cardiovascular morbidity, and infectious morbidity were our 4 primary outcome variables. Unless otherwise mentioned, mortality in this manuscript indicates the mortality except the ones that had occurred within 48 hours since the administration of the sedatives. Cardiovascular and infectious morbidity were judged with the help of the ICD-9 Code for diagnosis. The numbers in the parentheses show the dotless version of ICD-9 Code. Cardiovascular morbidity involved hypovolemia (27652), dialysis hypotension (45821), other iatrogenic hypotension (45829), atypical shock (78550), cardiogenic shock (78551), shock unrelated to trauma (78559), and cardiac and peripheral complications, unclassified (9971/9972). Infectious morbidity involved ventilator-associated pneumonia (99731),
infection of the central catheter (99931), bladder or urologic organ (99664, 99665), infection of the stoma (tracheostomy 51901, esophagostomy 53086, gastrostomy 53641, colostomy or enterostomy 56961), the implanted prosthesis (99660, 99661, 99662, 99663, 99666, 99667, 99668, and 99669), and other postoperative infections (99859).

We had set a guarantee period when counting all-cause in-hospital deaths. The reason for setting the guarantee period follows. We counted all-cause in-hospital deaths as deaths regarding the etomidate cohort. So acute deaths after the etomidate administration should be excluded because they generally have other causes other than the etomidate administration. Like the study of the ICU patients conducted in the year 2008 by Vinclair et al. [9], we applied the 48 hours of interval after the day of etomidate administration as the guarantee period. We excluded deaths which occurred during 48 hours after the cohort start-date when counting all-cause in-hospital deaths.

**Secondary Outcome Measures including Dose-Mortality Relationship with Exploration of Other Factors**

Secondary outcomes are supplementation of corticosteroid (n), vasopressor therapy (n), cortisol blood concentration measured at the morning after the cohort start-date (µg/dL), accumulated time of vasopressor therapy (h) which were summed up after the cohort start-date, ICU stay duration (day), total hospitalization duration (day), and dose-mortality relationship of etomidate.

To check the dose-mortality relationship that may exist in the etomidate cohort, factors that may influence the mortality were explored in the after-matching cohorts. We removed all other variables that contributed little to the overall regression model. Variables were selected by using the Akaike's Information Criterion (AIC)-based stepwise selection method in pursuit of the most parsimonious model. All variables used for calculating the propensity score were exploited again with logistic regression and stepwise-selection of the variables was performed. In the regression...
model using only variables that were selected, the relationship was established between the administered dose (every 0.1 mg/kg) of etomidate and all-cause in-hospital death. In the dataset, since the observed dose ranges were not far beyond 0.5 mg/kg, so neither the LD50 nor the LD95 were extrapolated.

**Blood Pressure Profile on the Cohort Start-Date**

Systolic blood pressures and mean blood pressures of the cohort start-date were compared between 2 cohorts.

**Data Manipulation and Analytic Tools**

After obtaining the rights to handle the MIMIC-III, the whole dataset was imported and re-built as a copy of the structured query language (SQL) database on a personal computer based on 64-bit-Darwin. Codes for the MIMIC-III shared by The Laboratory of Computational Physiology of Massachusetts Institutes of Technology (https://github.com/MIT-LCP/mimic-code/tree/master/concepts) were utilized. They included patients’ comorbidities, vasopressor use, ventilator days, and body weights and heights. Temporary tables were created using the SQL and batch-queried into the R version 3.5.5 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2019). We employed the R software for all the subsequent manipulations and analyses. We practiced all statistical inferences, focusing on the size of the effect (odds ratio or Cohen’s d) and its associated uncertainty (CI), which complied with the American Statistical Association’s 2016 Statement on P-values [10]. Odds ratios were calculated from the conditional maximum likelihood method in the primary outcome and secondary measures, except the dose-response estimation that was from the log-odds in logistic regression. To calculate the intervals, the alpha was adjusted at 98.75% (= 1 − (0.05 / 4)) for 4 primary outcome
measures, while 95% for other measures. To address the size of the effect, the odds ratio was adopted for incidence data and Cohen’s d for interval data.

**Results**

Top 20 diagnostic impressions for the admitted patients were obtained and listed by the after-matching cohorts (Supplemental Digital Content 2). The maximum blood pressures were higher, while the minimum blood pressures lower in the etomidate cohort (Table 1).

**Primary Outcome Measures**

Overall 6,690 of the 6,875 patients who survived for the first 48 hours after the study drug was administered. The odds for hospital mortality was 1.84 times higher in the patients receiving etomidate (OR 1.84 [98.75% CI; 1.42, 2.37]). Odds for the first 48-hr survival was 57% lower in etomidate cohort (0.43 [0.27, 0.73]). Odds for cardiovascular morbidity was not significantly lower in the etomidate cohort (0.86 [0.66, 1.12]) than the propofol cohort. Etomidate cohort showed 1.77 times higher infectious morbidity (1.77 [1.35, 2.31]) (Fig. 1).

**Secondary Outcome Measures**

Regarding the odds ratio, the etomidate cohort received corticosteroid replacement 1.82 times more frequently, and received vasopressor therapy 1.39 times more frequently. Total 3,399 cortisol measurements from the 1,341 patients (195 and 1,146 patients for the etomidate and propofol cohorts) were performed. Etomidate resulted in trivial decrement in the morning blood cortisol level (95% confidently, at most Cohen’s d = -0.30 mcg/dL). The cumulative vasopressor duration (68.1 vs. 42.7 hours), the total ICU stays (14.9 vs. 8.9 days), and the hospital days (23.1 vs. 16.7 days) were longer in the etomidate cohort (Table 2).
The administered dose of etomidate ranged from 0.02 to 0.50 mg/kg. Its mean was 0.19 mg/kg and median 0.19 mg/kg with Q1 and Q3 of 0.14 and 0.24. The odds for dose effect of etomidate for every 0.1 mg/kg increment was estimated 1.36 times higher (1.36 [1.23, 1.49]). These dose-effect estimates did not change before and after the removal of other variables using the AIC-based stepwise selection method (Figs. 2 and 3). Patients of the male gender, younger (under 86 years of age), not having lower BMI (over 18.5), with lower SOFA score (below 5.0), and free from preexisting adrenal insufficiency were found to be associated with better in-hospital survivals. Patients admitted as a not-elective type and admitted before mid-2008 were associated with poor in-hospital survival. The effects of all other potential factors are listed in Fig. 3.
Discussion

We found that a biological gradient is existing in the dose of etomidate used and mortality. Through this, it is hard to say that causality is existing, but we can say that increased etomidate dose is associated with increased mortality. This may work as a hint when establishing the causality. With the retrospective analysis which showed the dose-response relationship, we concluded that etomidate use is associated with increased mortality in a dose dependent manner, which might have the utmost importance to the intensivists.

Etomidate seemed to be used selectively in patients with wide fluctuations of the blood pressure. However, the use of etomidate didn’t salvage patients in the first 48-hr. The cardiovascular morbidity was not diminished despite the use of the etomidate. Moreover, the etomidate cohort had received vasopressor therapy more frequently and its cumulative vasopressor duration was longer. Conversely, using etomidate was associated with higher infectious morbidity and higher incidence of subsequent corticosteroid replacement, and the replacement was associated with higher death rate.

Our study showed dose-effect of etomidate on the mortality. Simple association does not imply causation. Defining the causal connection in modern medical research is not simple. Cause-and-effect can best be inferred from randomized controlled trials. Plus, according to the Bradford Hill criteria which provides evidence of a causal relationship, when greater exposure leads to greater incidence of the effect or an inverse proportion is observed, it can be said that there’s a hint of a causal relationship. However, it should be noted that, in most of the previous studies which tried to show the relationship between etomidate and high mortality, they have ignored the dose-effect relationship. In this study, we adopted the propensity score matching procedure and calculated
dose–mortality relationship instead of using randomizations. We have established a relationship between etomidate dose and mortality, but we do not intend to assert that a solid causal relationship is exiting only by itself. However, this is an unprecedented finding when considering the miscellaneous and multi-factor characteristics of deaths of patients undergoing respiratory therapy. Moreover, our discoveries would shed a light of hope in future causality research regarding deaths in ICU patients given etomidate.

There were another 2 notable aspects regarding our calculated values of the dose-effect. First, the estimates of the calculated dose-effect remained unaltered in 2 decimal accuracy amid the vigorous stepwise-selection of the variables (1.36 [1.23, 1.49] vs. 1.36 [1.23, 1.49]), thereby indicating that the dose-effect of etomidate was independent of other factors. Second, calculated dose-effect was 1.85, which meant that odds for death was increased 1.85 times per every 0.1 mg/kg of etomidate. Therefore, we squared the result, 1.85 (1.36 × 1.36), to calculate the odds for the well-accepted dose of the etomidate (0.2 mg/kg), and it came with a result which was almost the same with 1.84, the odds ratio for mortality of the etomidate cohort presented in Fig. 1. The estimates derived from 2 different processes that were proved to be same means that our finding was more reliable.

There are some limitations in our study due to its retrospective nature. First, the MIMIC-III dataset does not clearly state why the physicians prescribed the sedatives. We only gathered prescriptions of etomidate and propofol which were prescribed on the day of ventilator therapy initiation. However, we cannot clearly indicate whether the sedatives were used for facilitating intubation or for other purposes. We selected who were prescribed sedatives on the first day of the mechanical ventilation. Therefore, we could infer that the intensivists used sedatives to the patients who needed mechanical ventilation.
Second, the MIMIC-III dataset does not explain the physician’s intention of choosing the etomidate over the other drug. We had to assume that intensivists were attracted to hemodynamic stability provided by etomidate when the patients were in unfavorable condition. The blood pressure fluctuations were not included in the initial list of variables for the matching procedure. Because we wanted to emphasize this significant difference by dealing this matter once again in this section. As we presented in the Table 1, the average systolic blood pressure and average mean blood pressure of the 2 cohorts were almost the same, they showed no big differences. The difference they showed was the fluctuations in the systolic blood pressures (SBP) which was wider in the etomidate cohort. We assumed that the intensivists had chosen to use etomidate in the patients who were expected to show unstable vital signs after the administration of sedatives. In the case of SBP, the fluctuations were 82 mm Hg vs. 68 mm Hg in the etomidate cohort vs. propofol. It means the etomidate cohort had showed more severe systolic blood pressure fluctuations. However, the mean blood pressure was almost the same between the 2 cohorts, and the difference of the extent of the fluctuation of the two groups was 14 mm Hg. This greater blood pressure fluctuation means unstable hemodynamic state and this may have affected the intensivist’s decision on choosing sedative that minimally affects the vital signs.

In conclusion, in the mixed-diagnoses of ICU patients underwent ventilatory therapy, etomidate usage had a significant effect on mortality with dose dependent manner. It is not helpful to use etomidate in a hope to improve the initial survival of the ICU patients showing unstable vital signs, because the odds of the survival of the first 48 hours in the etomidate cohort was 57 % lower. Though etomidate is known to provide favorable hemodynamic state, it is suggestive of failure of improving the survival of the first 48-hr. Rather, it is associated with increased overall mortality in
a dose-dependent manner.
Supplements

Full analytic code was developed by the authors and is freely available at https://github.com/ylee03/etomidate_kja.
References


**Table 1.** Blood Pressure Profile of the Cohort Start Day

<table>
<thead>
<tr>
<th></th>
<th>Etomidate (n = 625)</th>
<th>Propofol (n = 6,250)</th>
<th>Cohen’s d</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
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<td>118.9</td>
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<td>Minimum</td>
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<td>-0.3</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Maximum</td>
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Cohen’s d = (etomidate mean - propofol mean) / SD
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<th>Outcome Measure</th>
<th>Etomidate (n = 625)</th>
<th>Propofol (n = 6,250)</th>
<th>Odds ratio</th>
<th>Cohen’s d*</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
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<td>232</td>
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<td>Vasopressor (n)</td>
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<td>1.16</td>
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<td>Cortisol level (µg/dl)†</td>
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<td>Vasopressor duration (h)</td>
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<td>Hospital stay (day)</td>
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<td>16.7</td>
<td>-</td>
<td>0.42</td>
<td>0.34</td>
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</tr>
</tbody>
</table>

*Cohen’s d = (etomidate mean - propofol mean) / SD

†Total 3,399 cortisol measurements in 1,341 patients (195 and 1,146 patients for the etomidate and propofol cohorts)
Fig. 1. Four Primary Outcome Measures in the After-Matching Cohorts (N = 625 vs. 6,250). Odds ratios and those 98.75% confidence intervals.
Fig. 2. Etomidate Dose-Effect on Mortality Before the Variable Selection. All variables are included tentatively to explain the mortality with the dose of etomidate.
Fig. 3. Dose-Mortality Relationship with the Selected Factors. After the stepwise selection of variables, the effect of the dose of etomidate on mortality is adjusted.
List of Supplemental Digital Contents

Supplemental Digital Contents 1.  Patients Characteristics and Preexisting Conditions Before and After Propensity Score Matching

Supplemental Digital Contents 2.  Top 20 Diagnoses at Admission